LEUKEMIA

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Learning Objectives

By the end of this lecture the student must be able to:

- Define leukemia & identify it's etiology
- Discuss the definition, Pathophysiology , signs and symptoms & Lab diagnosis of:
  - *Acute lymphatic leukaemia (ALL)*
  - *Acute Myelogenous Leukaemia (AML)*
  - *Chronic lymphocytic Leukaemia (CLL)*
  - *Chronic Myelogenous leukaemia(CML)*

- Refer to Essential Hematology book, 6th edition , page (179 -199) & (224- 244)

LEUKEMIA

Definition

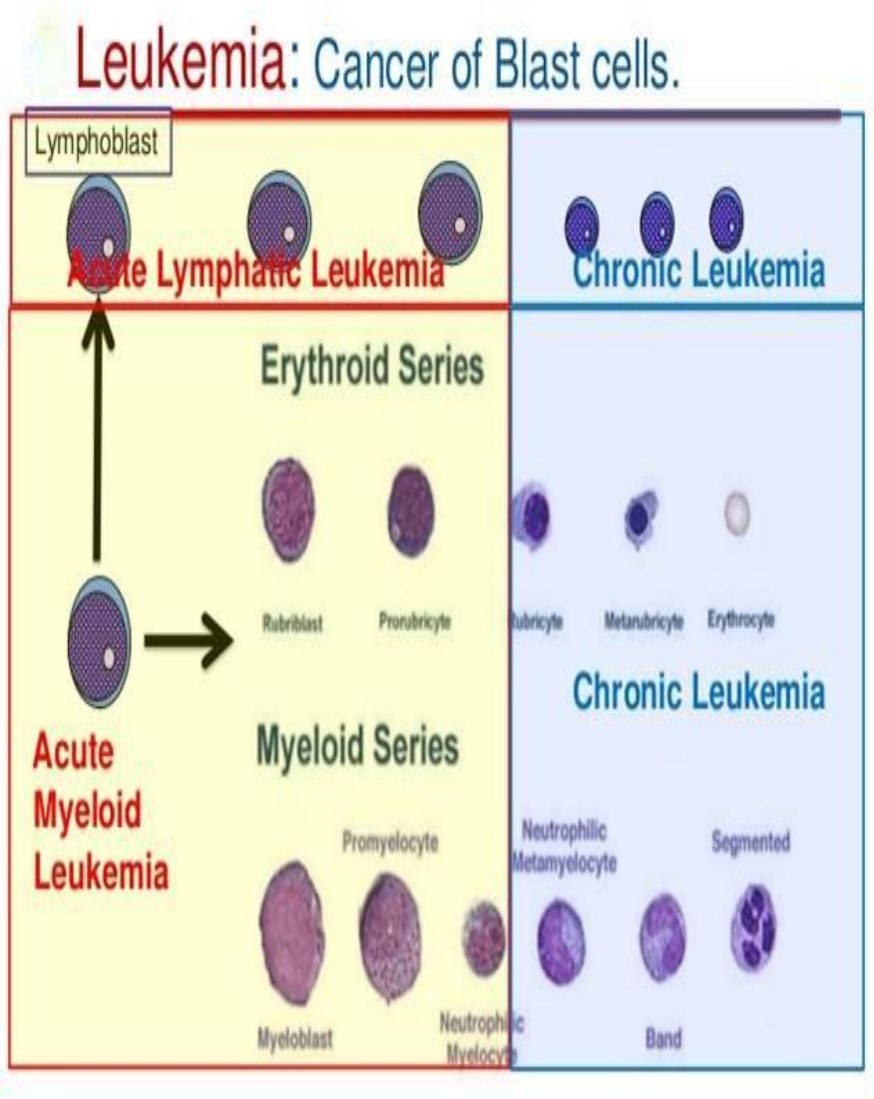
Group of malignant disorders of the hematopoietic tissues characteristically associated with increased numbers of white cells in the bone marrow and blood.

Aetiology (not known but PPF are known);

- Combination of predisposing factors including genetic (Hereditary , chromosomal fragility or abnormality as Down syndrome) and environmental influences (viral).
- Chronic exposure to chemical such as benzene
- Radiation exposure.
- Cytotoxic therapy of breast, lung and testicular cancer.

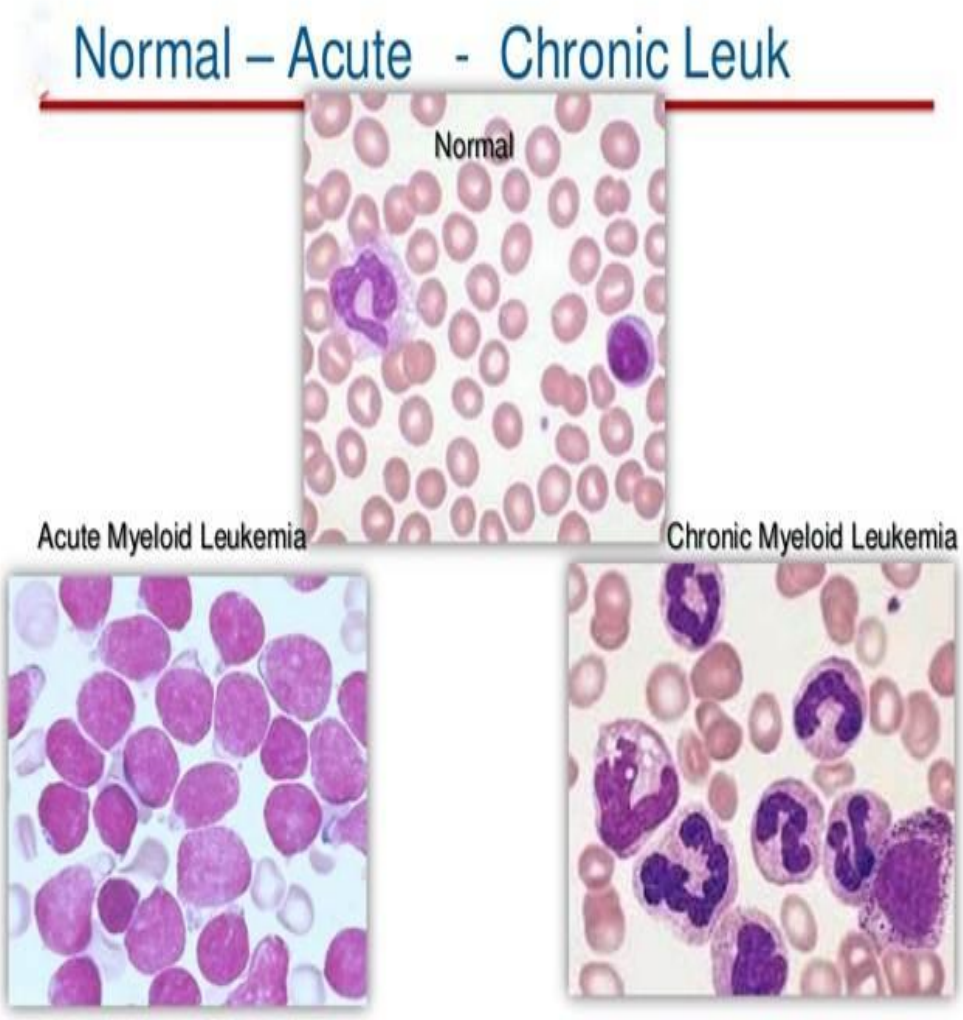
Introduction to leukemia

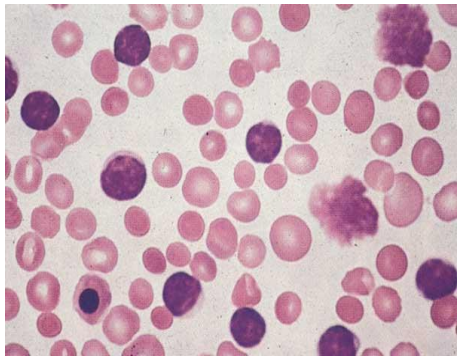
- It may involve any of the cell lines or a stem cell common to several cell lines.
- Therefore, there are four basic types of leukemia:
  - Acute myelocytic leukemia – AML
  - Acute lymphocytic leukemia – ALL
  - Chronic myelocytic leukemia – CML
  - Chronic lymphocytic leukemia – CLL
- As the disease progresses, leukemic cells accumulate in the bone marrow, blood, and organs, displacing normal progenitor cells and suppressing normal hematopoiesis



Introduction to Leukemia

- Leukemia are classified into 2 major groups
  - **Chronic**
    - Insidious onset,
    - Less aggressive,
    - Cells involved are usually more mature cells
  - **Acute**
    - Usually rapid onset,
    - Very aggressive,
    - Cells involved are usually poorly differentiated with many blasts.



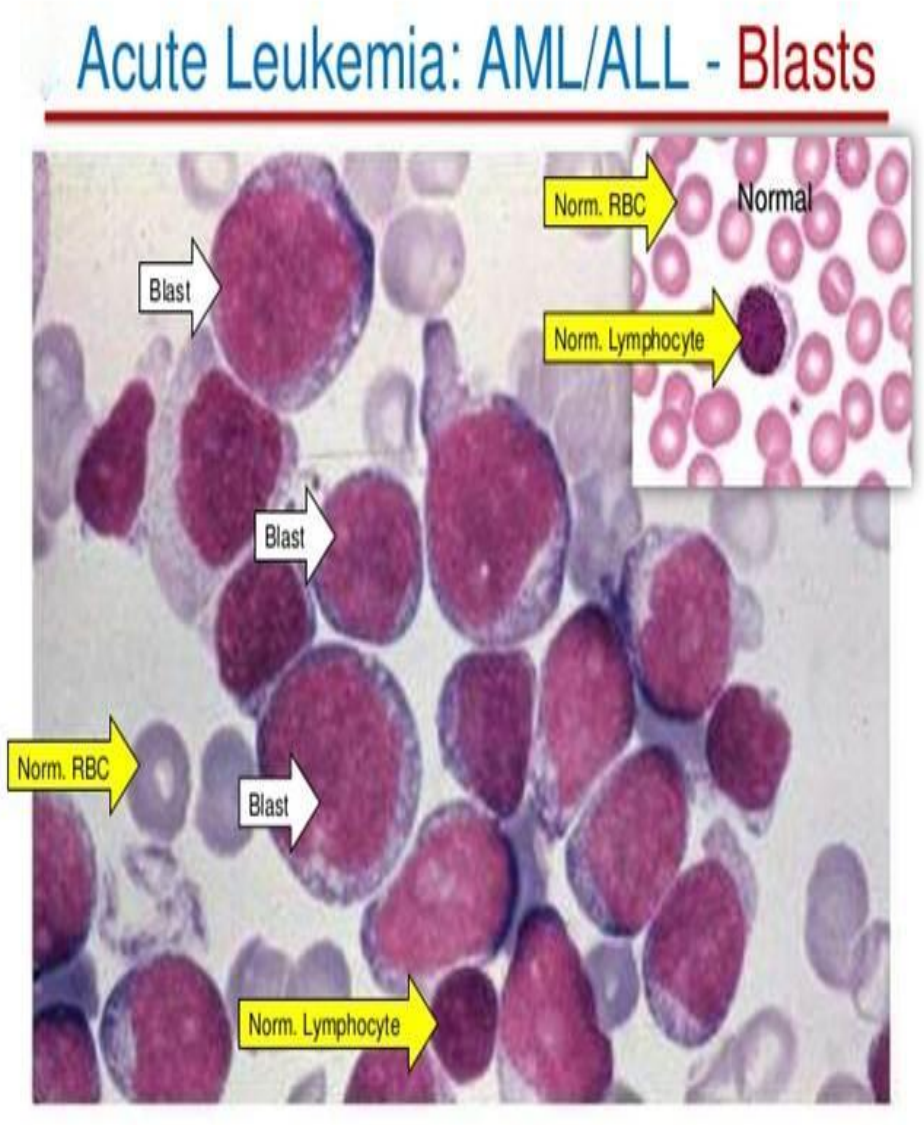


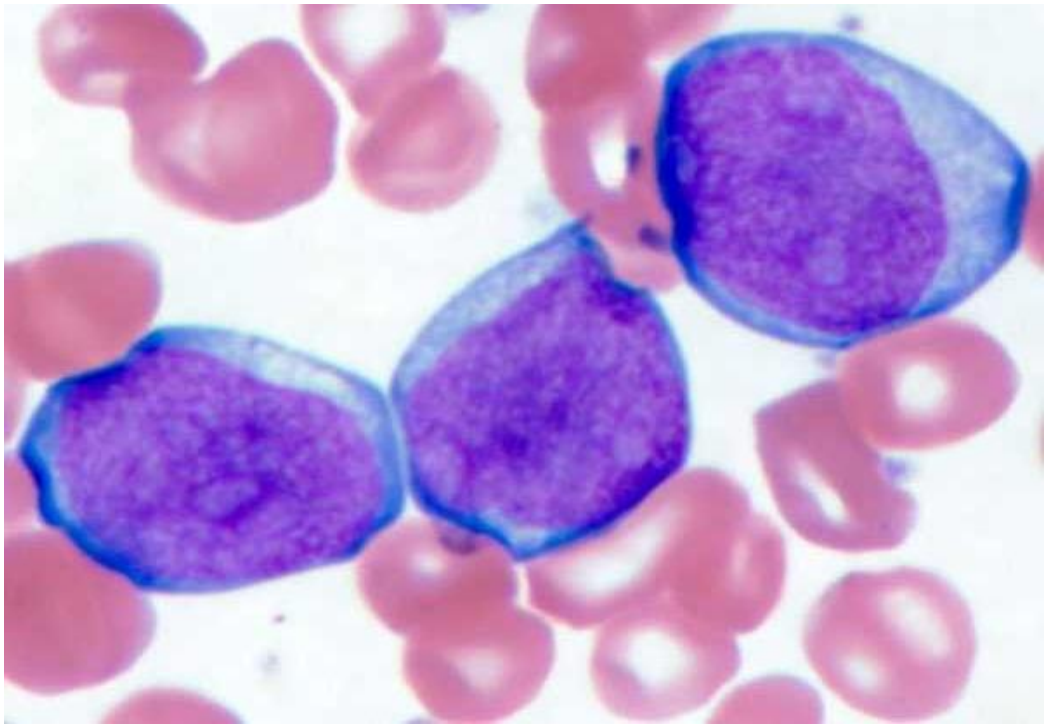
Leukemia Classification

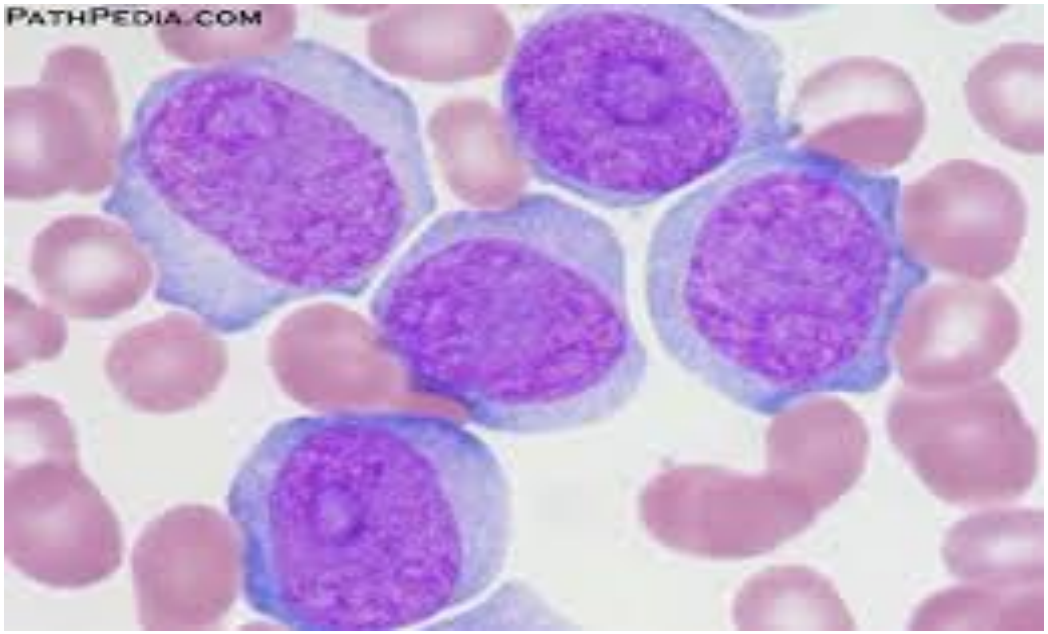
- **Acute Leukemias:** weeks to months.
  - Acute Myeloid Leukemia – **AML** - Adults
    - **Many Subtypes:** M0, M1 to M7
  - Acute Lymphoid Leukemia – **ALL** - Children
    - **Many Subtypes:** L1, L2 & L3
- **Chronic Leukemias:** Years.
  - Chronic Myeloid Leukemia- **CML**- Adults
  - Chronic Lymphoid Leukemia - **CLL** –Old age
    - Many subtypes:

Acute Leukemia

- Acute leukemia is characterized by an abnormal proliferation and arrest in maturation at the **primitive blast** stage.
- It may involve stem cell or one of cell progenitor.







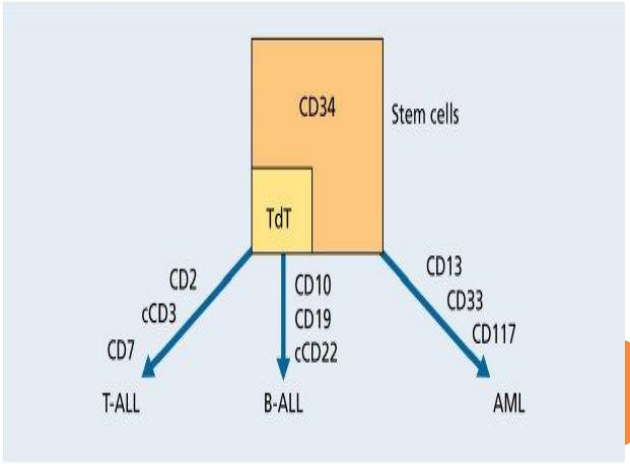
Two main forms of acute leukemia:

Acute myeloid leukemia

Usually a malignancy of the myeloblast

Acute lymphoblastic leukemia

A cancer at the earliest stages of lymphocyte maturation



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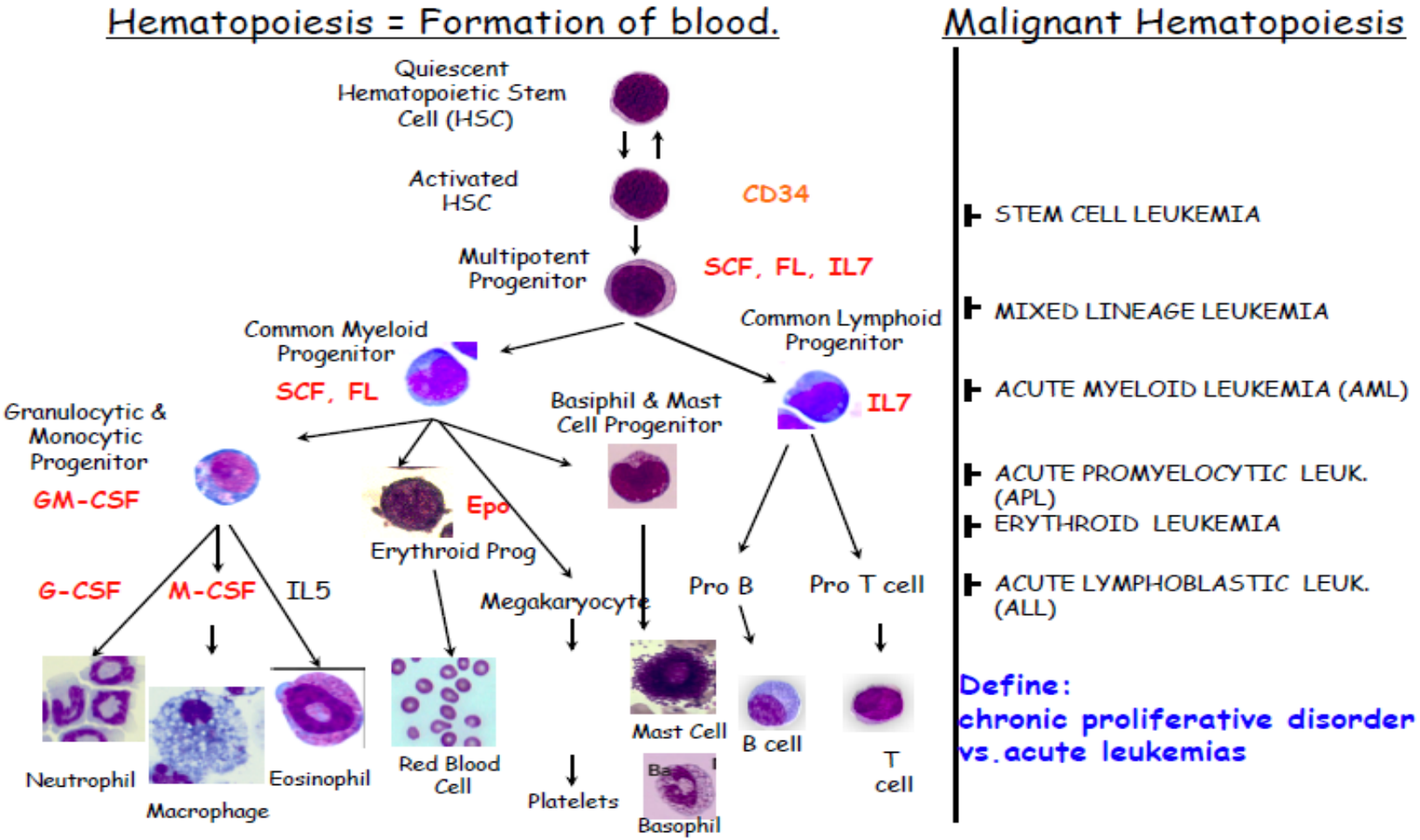
AML; M1- M7 Subtypes



Leukemias arise in committed progenitors, Have intrinsic differentiation blocks
Mitogenic oncogenes cooperate (SCFR, FLT3, Ras, Akt, PI3-kinase, PTEN)

Acute Leukemia – Clinical Presentation

- **Short course** of symptoms
  (within 3 months)
- Bone marrow failure – **pancytopenia**
  (anemia, infection, bleeding)
- **> 20% blasts in bone marrow**
- Blasts in peripheral blood in 90% cases
- **Bone pain** & tenderness.
- Hypermetabolism:
  - **↑LDH.**
  - **↑uric acid**.
- **Fatigue, fever, loss weight, lassitude**

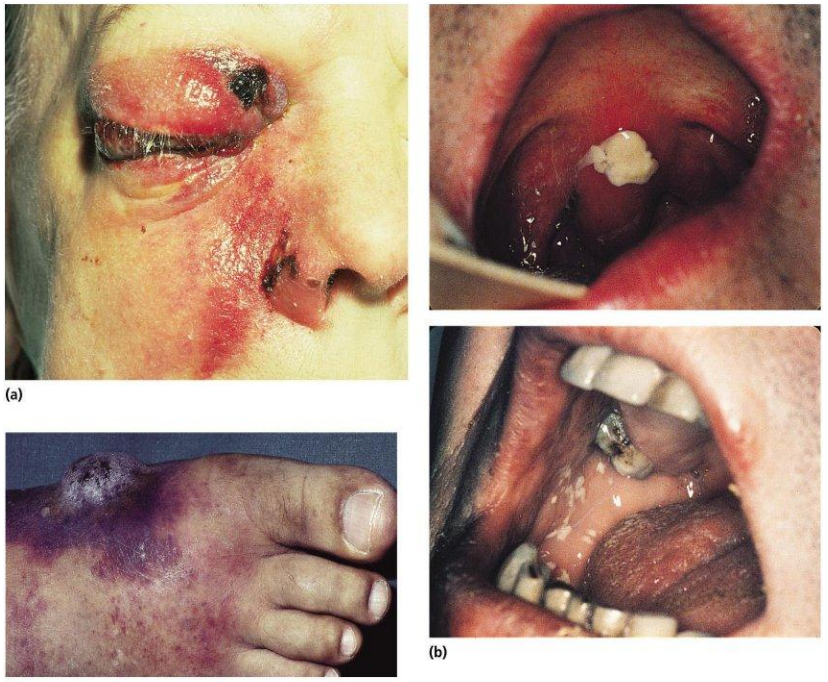


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Figure 13.2 **(a)** An orbital infection in a female patient (aged 68 years) with acute myeloid leukaemia and severe neutropenia (haemoglobin 8.3 g/dL, white cells 15.3 × 10^9/L, blasts 96%, neutrophils 1%, platelets 30 × 10^9/L). **(b)** Acute myeloid leukaemia: top: plaque *Candida albicans* on soft palate; lower: plaque *Candida albicans* in the mouth, with lesion of herpes simplex on the upper lip. **(c)** Skin infection (*Pseudomonas aeruginosa*) in a female patient (aged 33 years) with acute lymphoblastic leukaemia receiving chemotherapy and with severe neutropenia (haemoglobin 10.1 g/dL, white cells 0.7 × 10^9/L, neutrophils <0.1 × 10^9/L, lymphocytes 0.6 × 10^9/L, platelets 20 × 10^9/L).

Acute leukaemia; Clinical presentation

Signs and symptoms

Anaemia, bleeding, infection

Clinical manifestation	Clinical manifestation
▪Fever ▪Pallor ▪Bleeding ▪Anorexia ▪Fatigue ▪Weakness ▪Bone, joint and abdominal pain ▪Increase intracranial press.	▪Generalized lymphadenopathy ▪Infection of respiratory tract ▪Anaemia and bleeding of mucus membrane ▪Ecchymoses ▪Weight loss ▪Hepatomegaly ▪Mouth sore

Clinical presentation:

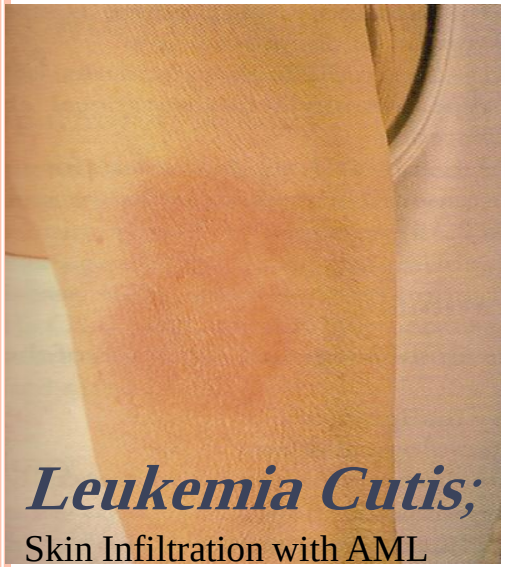
- **Organ infiltration** → Tumor lysis syndrome … Renal failure
  - Splenomegally.
  - Hepatomegally.
  - Lymphadenopathy.
  - CNS:5-10% of patient with ALL
  - L mediastinal tumoral mass
  - L CNS infiltration

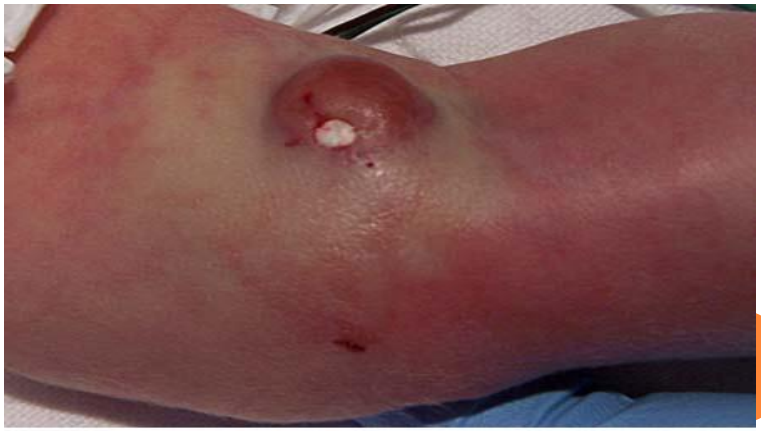
  } More common with ALL than AML.

  - M2 : Chloroma:-presents as a mass lesion ‘tumor of leukemic cells’
  - M3 : DIC
  - M4/M5 : Infiltration of soft tissues, *gum infiltration*, skin deposits ,Meningeal involvement-headache, vomiting, eye symptoms

Clinical symptoms/Physical Findings

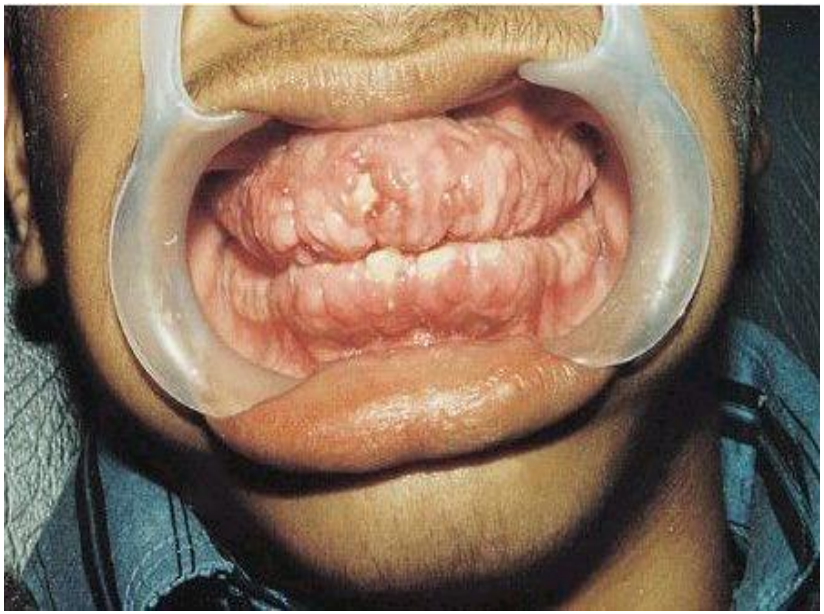
- Leukostasis (WBC > 100,000)
- Extramedullary disease (ie, myeloid sarcoma)
  - Can also have involvement of lymph nodes, intestine, mediastinum, ovaries, uterus





Source: Lichtman MA, Shafer MS, Felgar RE, Wang N:
Lichtman's Atlas of Hematology: http://www.accessmedicine.com

Gingival Infiltration
in Monocytic; (AML M4- eos)Variant of AML

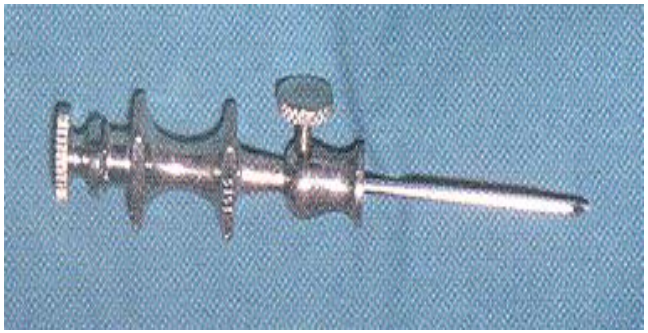


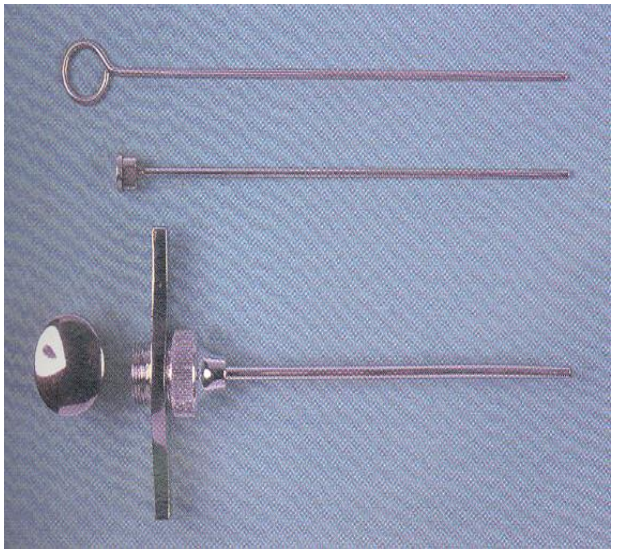
Gum hypertrophy

- Mani, A, Lee, DA. Leukemic Gingival Infiltration. N Engl J Med 2008; 358(3): 274. Copyright ©2008 Massachusetts Medical Society

Acute leukemia - Diagnosis

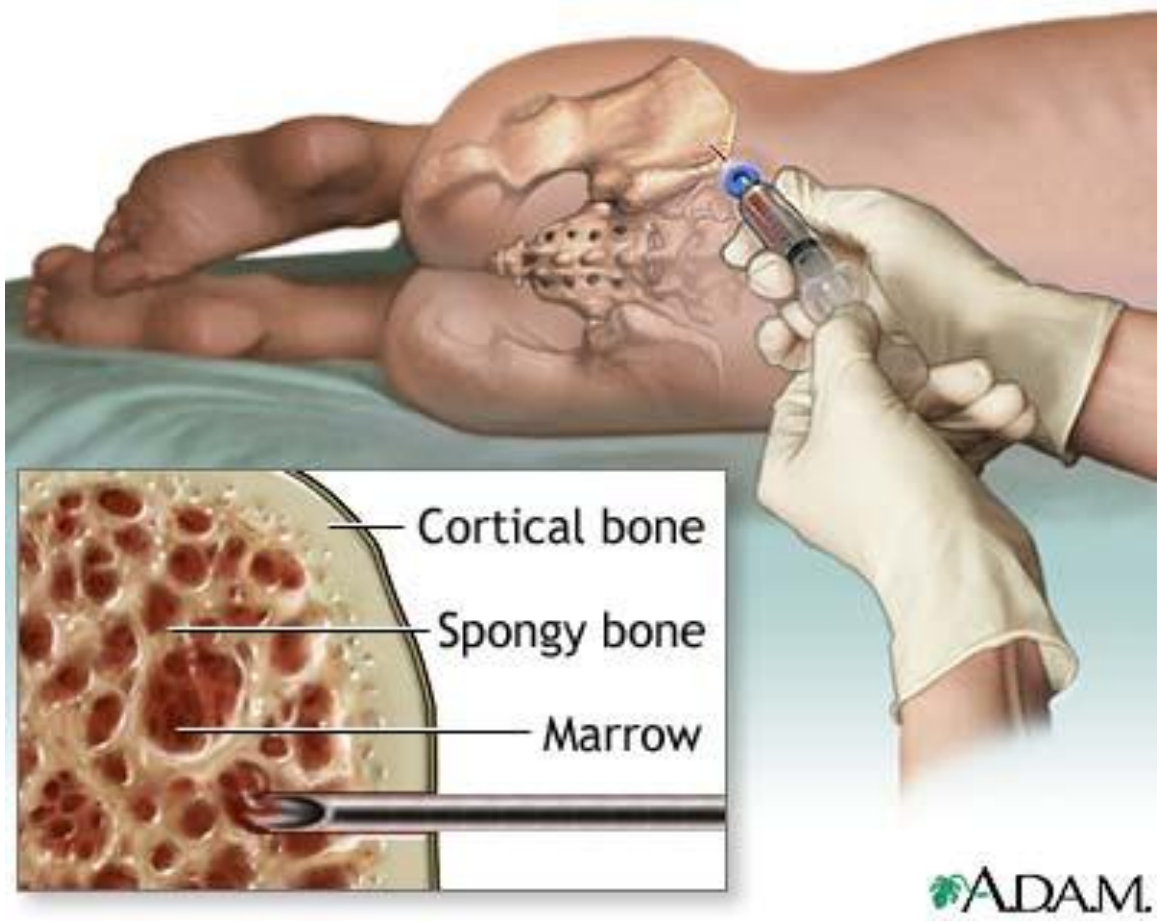
- Lab evaluation
  - The lab diagnosis is based on two things
    - Finding a significant increase in the number of immature cells in the bone marrow (>20% blasts is diagnostic)
    - Identification of the cell lineage of the leukemic cells





Jemshidi trephine & Salah aspiration needle

Bone Marrow Aspiration/Biopsy



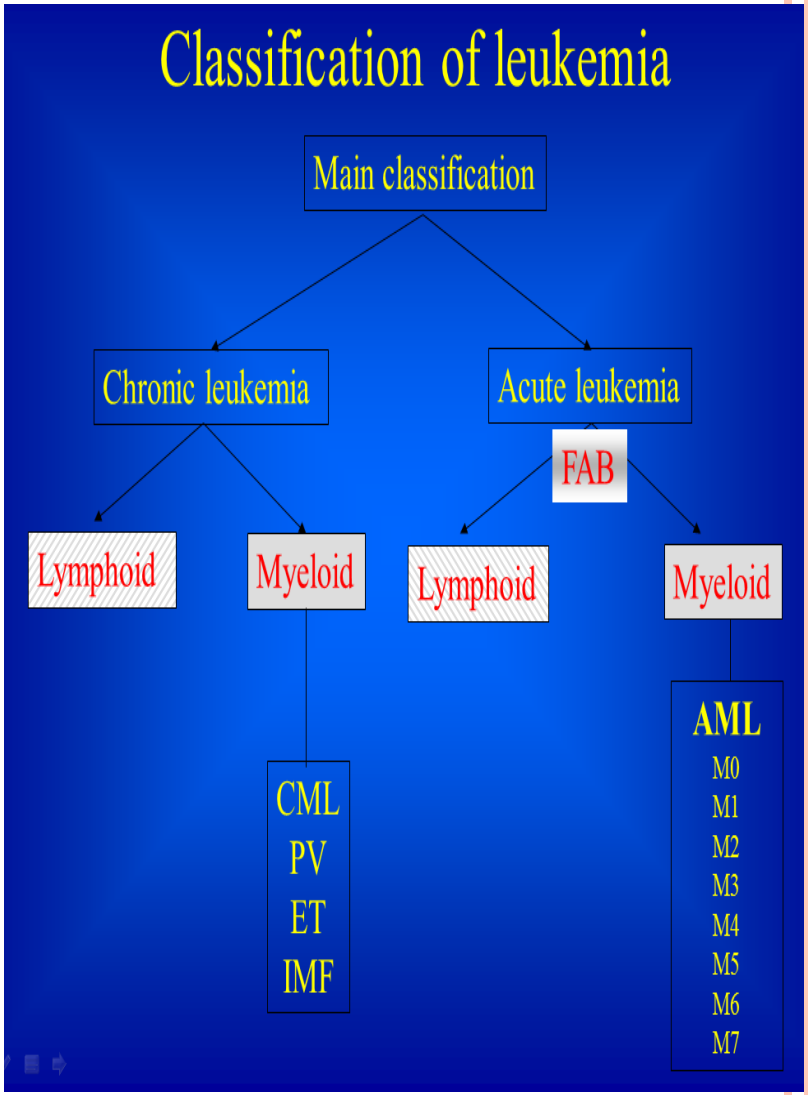
ACUTE LEUKEMIA – CLASSIFICATION & DIAGNOSIS

- Diagnosis and classification of the immature cells involved may be done by :
  - Morphology
  - Cytochemistry
  - Immunophenotyping
  - Cytogenetic

- <u>Classification:</u>

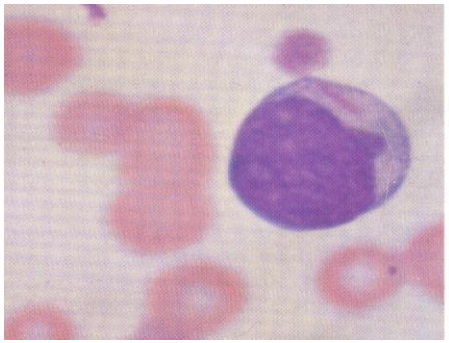
  3 groups of acute leukemias:

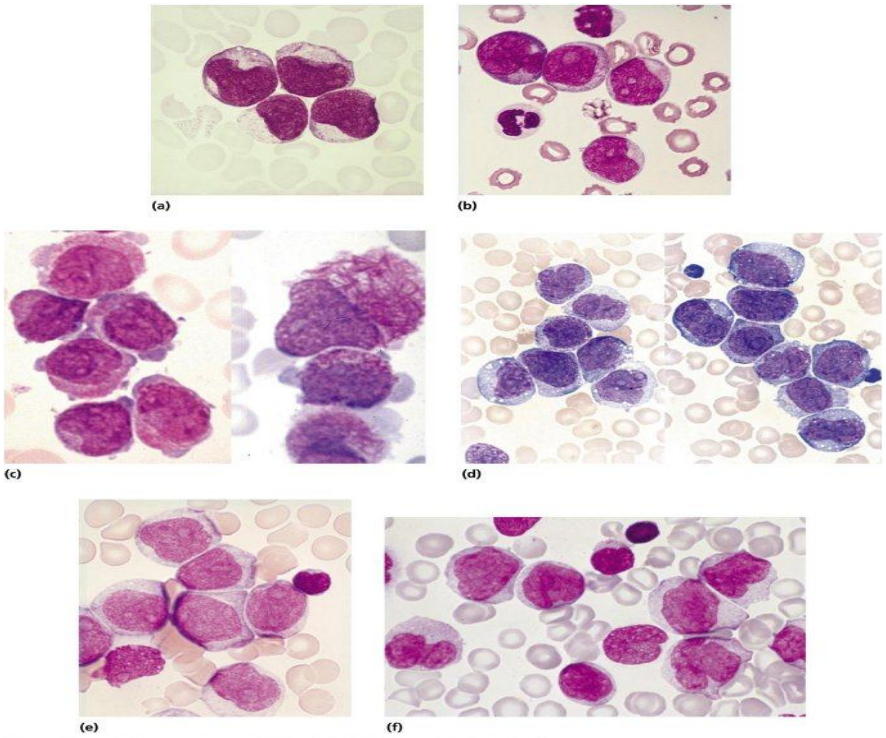
  - AML *(M1 –M6).*
  - ALL *(L1-L3).*
  - Biphenotypic leukemias *(mixed lineage)*



DIAGNOSIS; MORPHOLOGIC

- **French American British (FAB) AML classification:** (M1 –M6) – the myeloblast is a large blast with a moderate amount of cytoplasm, fine lacey chromatin, and prominent nucleoli. 10-40% of myeloblasts contain **auer rods**.





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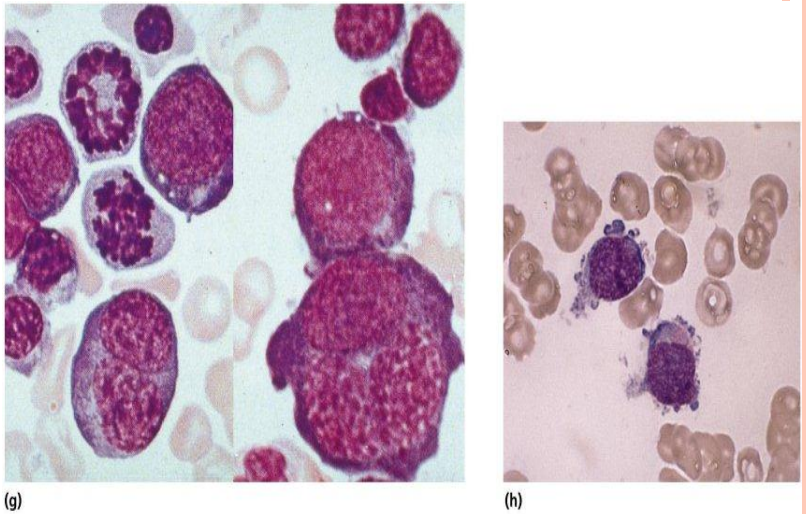

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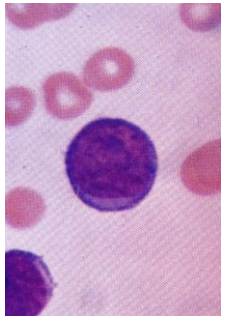
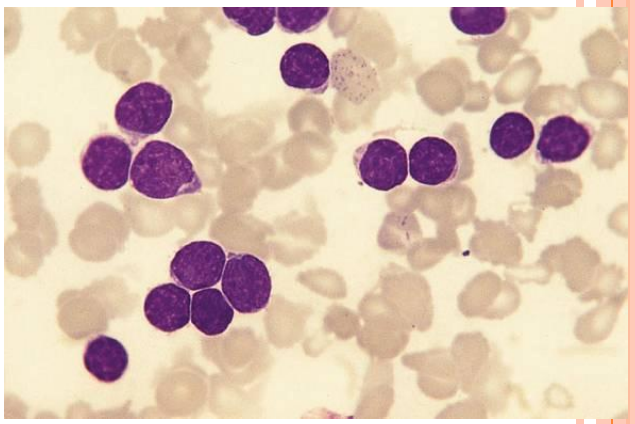
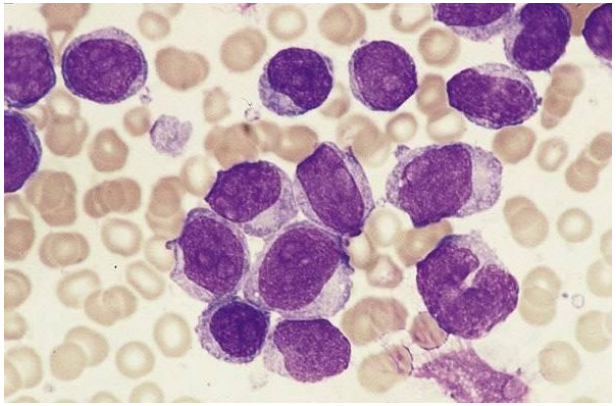
Diagnosis; Morphologic

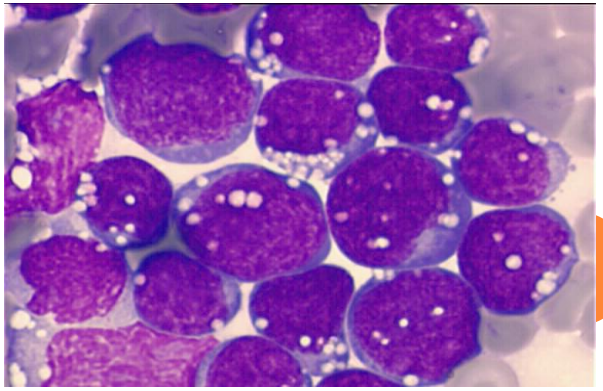


- ALL (L1-L3) – in contrast to the myeloblast, the lymphoblast is a small blast with scant cytoplasm, dense chromatin, indistinct nucleoli, and no auer rods



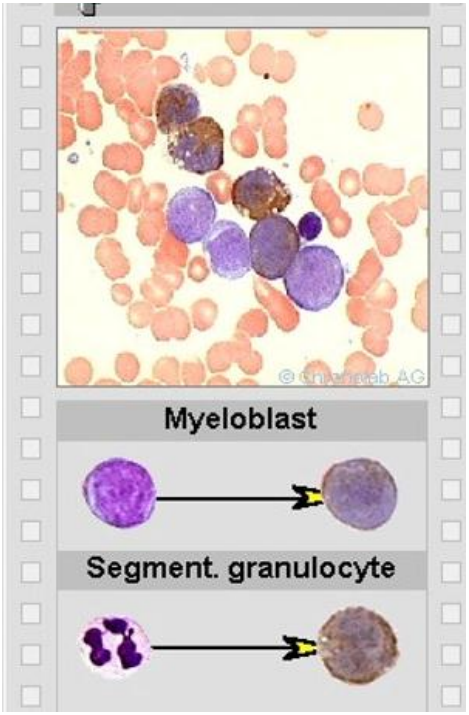
- French American British (FAB) Classification:
  - L1: small uniform blasts
  - L2: larger, more variable sized blasts
  - L3: uniform cells with basophilic and sometimes vacuolated cytoplasm (mature B cell ALL)

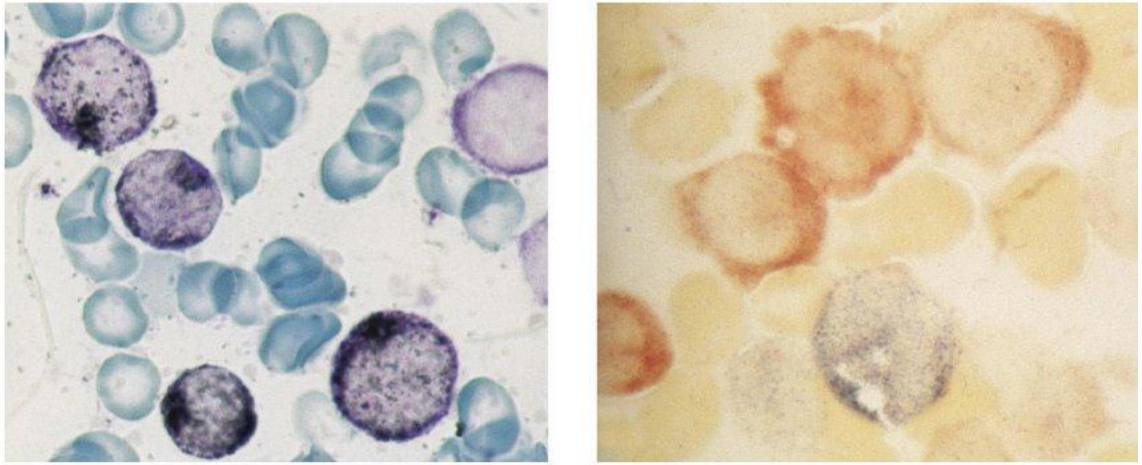




Diagnosis; Cytochemistry

- Cytochemistry – help to classify the lineage of a leukemic cell (myeloid versus lymphoid)
  - E.g. Myeloperoxidase – is found in the primary granules of granulocytic cells starting at the late blast stage. Monocytes may be weakly positive.





(a) (b)

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Figure 13.5 Cytochemical staining in acute myeloid leukaemia. **(a)** Sudan black B shows black staining in the cytoplasm. **(b)** Myelomonocytic: non-specific esterase/chloracetate staining shows orange-staining monoblast cytoplasm and blue-staining (myeloblast) cytoplasm.

Prognosis in AML

Prognostic Factors:

- Age at diagnosis *(>60 is unfavorable)*
- Chromosomal findings

(NPM is favorable, deletion of chromosome 7 is unfavorable).

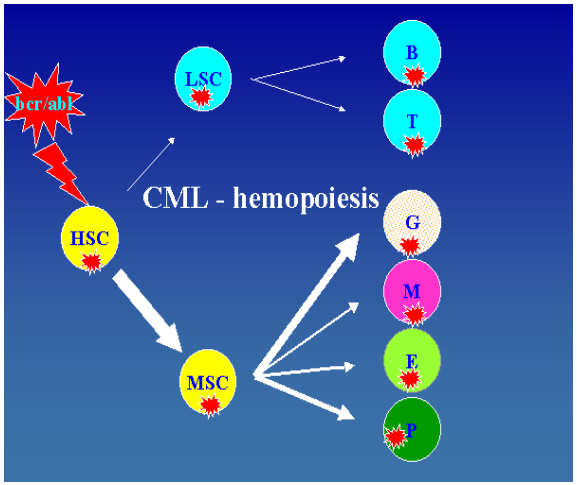
- Bone marrow response to remission induction

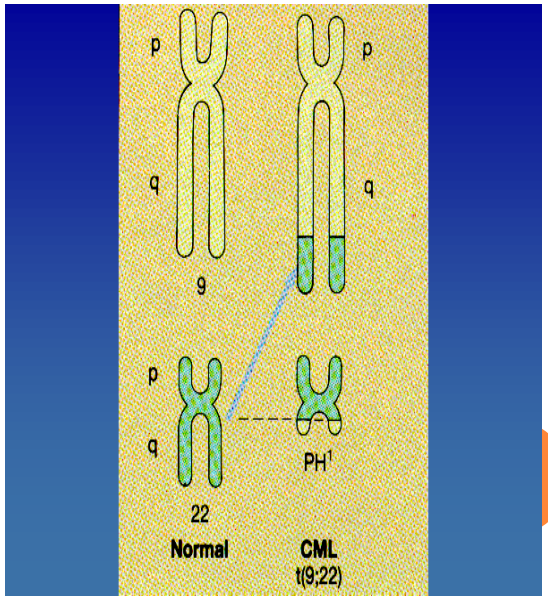
Prognosis in ALL

- **Age**, *(Patients <1 y and <13 y have a poor prognosis)*
- **WBC count**, *(If the WBC count is > 20 x 10^9/L at presentation the prognosis is poor)*
- **Cell type** *(T cell ALL has a poorer prognosis than B cell ALLs)*
- **Cytogenetic abnormalities**,
- **Time to clear blasts from blood**,
- **Remission time**
- **CNS involvement**

CHRONIC MYELOID LEUKAEMIA

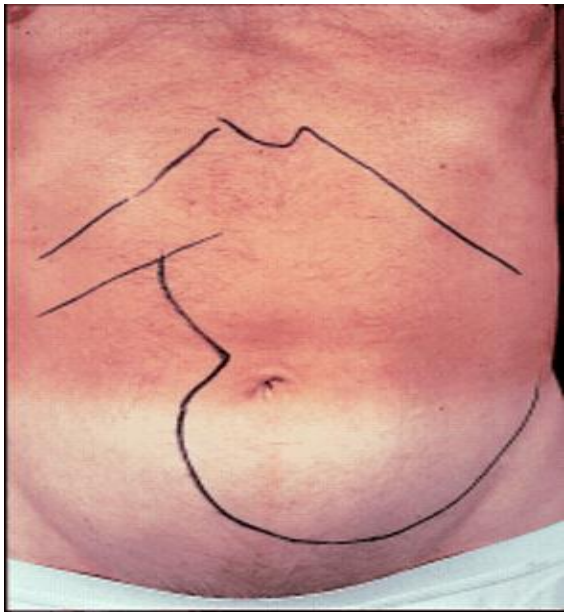
- It is a clonal disorder of a pluripotent stem cell.
- It may occur at any age commonly between 40-60 Y.
- All cases of CML have a translocation t(9;22). This leads to the oncogene ABL1 being moved to the BCR gene on chromosome 22 and generates the philadelphia chromosme.
- The resulting chimeric BCR-ABL1 gene codes for a fusion protein with tyrosine kinase activity.





CLINICAL FEATURES

- The clinical features include anaemia, bleeding & splenomegly.
- There is usually a marked neutrophilia with myelocytes and basophils seen in blood film.
- Hyperleukocytosis
  - Thrombosis
  - Gout
- It may be transformed to an accelerated phase or acute leukaemia.



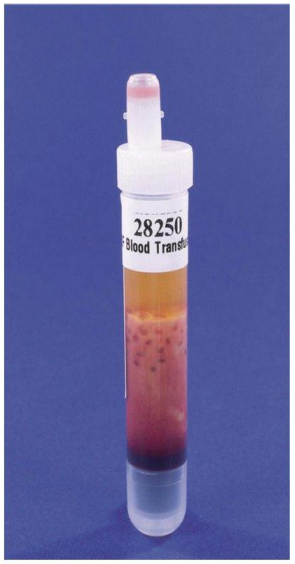
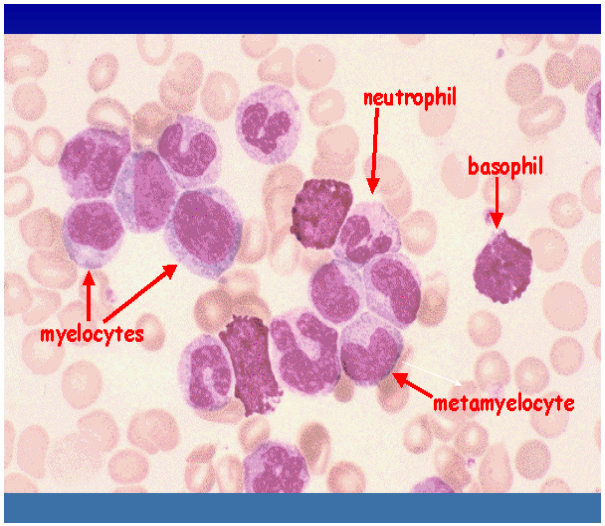


Figure 14.2 Chronic myeloid leukaemia: peripheral blood film showing a vast increase in buffy coat. The white cell count was 532 × 10^9/L.

CHRONIC MYELOID LEUKAEMIA MUST BE DIFFERNTIATED FROM 2RY **REACTIVE CAUSES; SEVER INFECTION**



Lab features

- Peripheral blood film
  - Anaemia
  - **Leukocytosis** (usu >25 x 10^9/L, freq> 100 x 10^9/L
  - WBC differential shows granulocytes in **all stages of maturation**
  - **Basophilia**

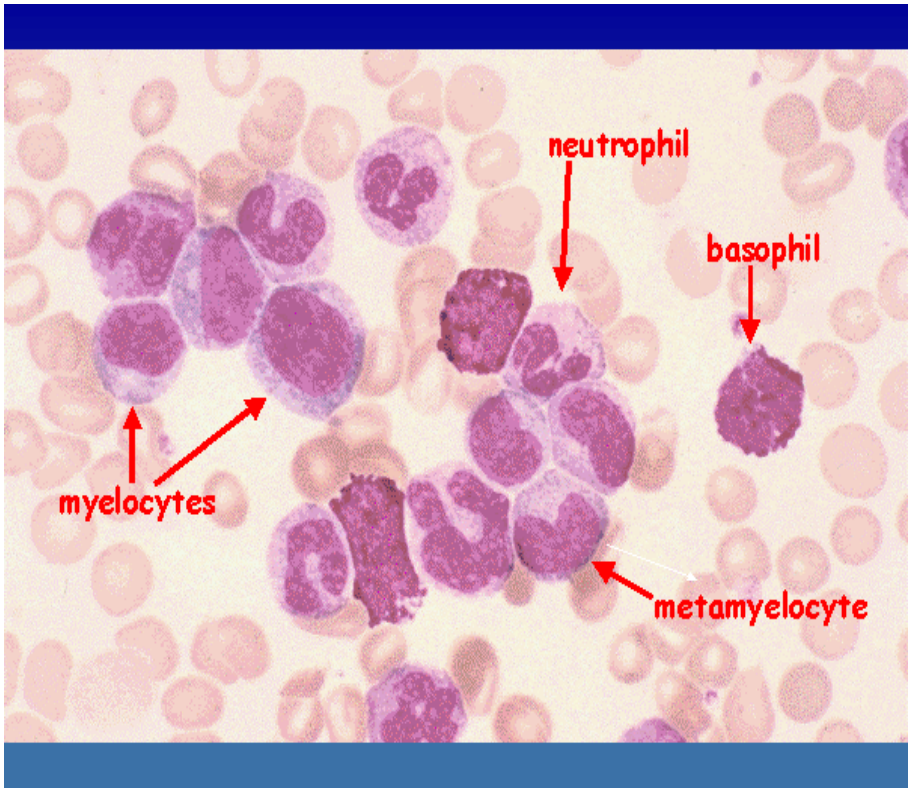
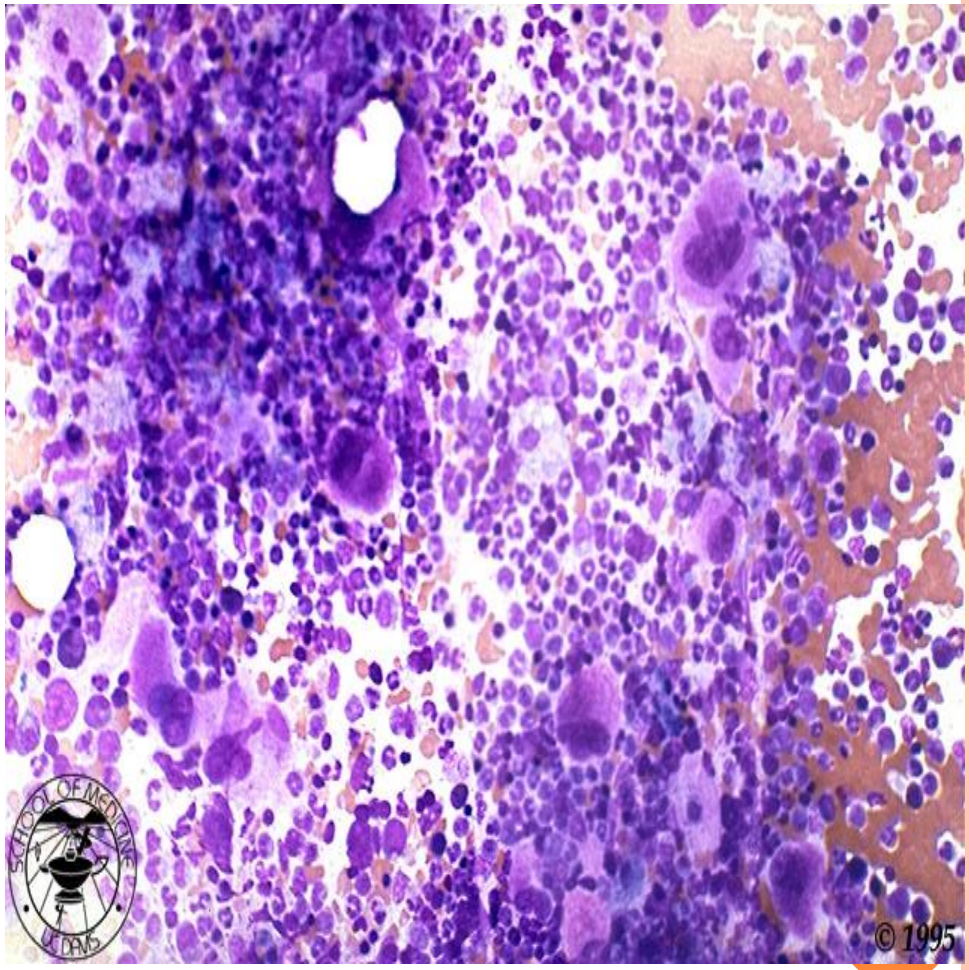


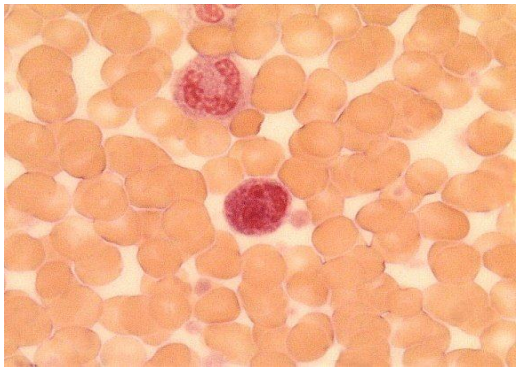
Figure 14.3 Chronic myeloid leukaemia: peripheral blood film showing various stages of granulopoiesis including promyelocytes, myelocytes, metamyelocytes and band and segmented neutrophils.

Lab features

- Bone marrow
  - Hypercellular
  - Myeloid: erythroid ratio increase
  - Myelocyte predominant cell, blasts <10%
  - Megakaryocytes increased & dysplastic

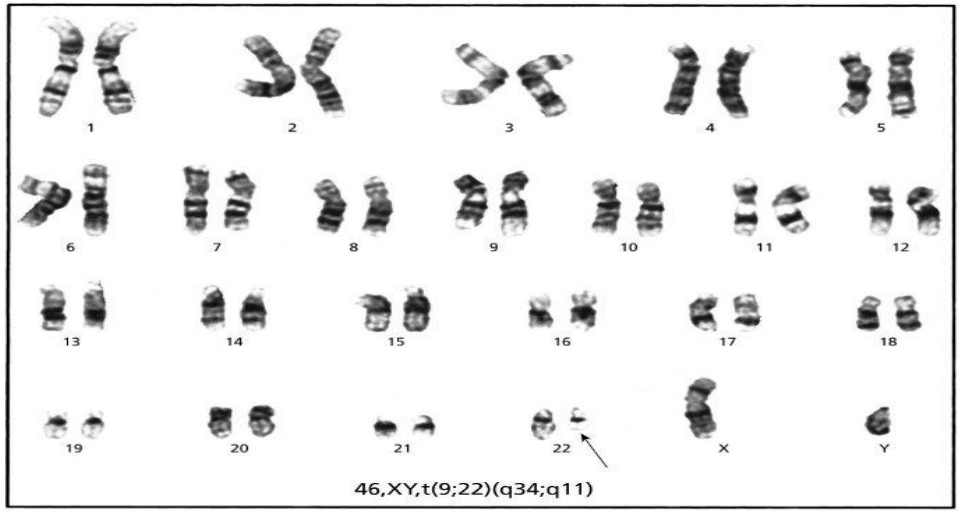


OTHER LAB FEATURES :



- NAP reduced
- Serum uric acid increased
- Lactate dehydrogenase increased
- Cytogenetic : Philadelphia chromosome

- **Ph +ve chromosome in CML a good prognostic factor.**



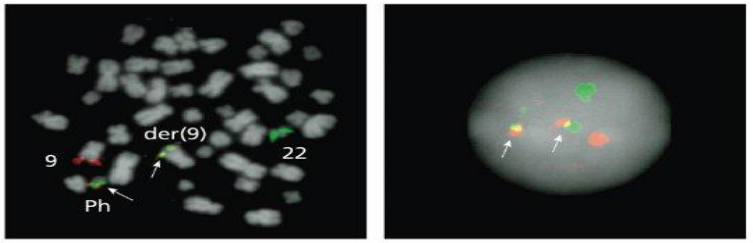


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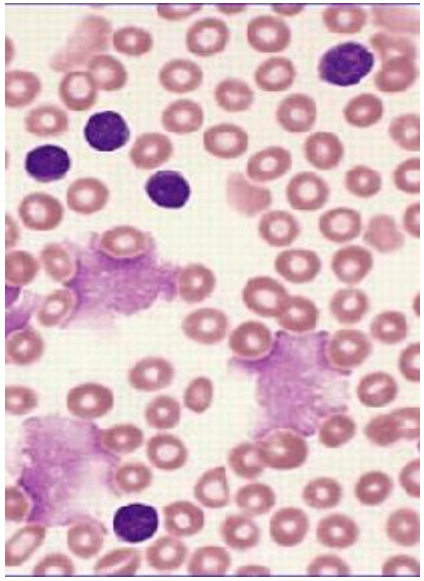
Figure 14.1 (*Continued*) **(d)** Karyotype showing the t(9; 22) (q34; q11) translocation. The Ph chromosome is arrowed. **(e)** Visualization of the Philadelphia chromosome on: (i) dividing (metaphase); and (ii) quiescent (interphase) cells by fluorescence *in situ* hybridization (FISH) analysis (ABL probe in red and BCR probe in green) with fusion signals (red/green) on the Ph and der(9) chromosomes. (Courtesy of Dr Ellie Nacheva)

Chronic lymphocytic Leukaemia (CLL)

- It is characterized by **clonal** proliferation of small, abnormal , mature B lymphocytes, often leading to decreased synthesis of immunoglobulin and cellular immune dysfunction (autoimmune).
- The number of mature lymphocytes in peripheral blood smear and bone marrow, lymph node & spleen are greatly increased.
- In most cases, the cells are **monoclonal** B lymphocytes that are CD5+. T cell CLL can occur rarely.
- There is some overlap with non- Hodgkin lymphoma.



Clinical Manifestation

Usually there is no symptoms.

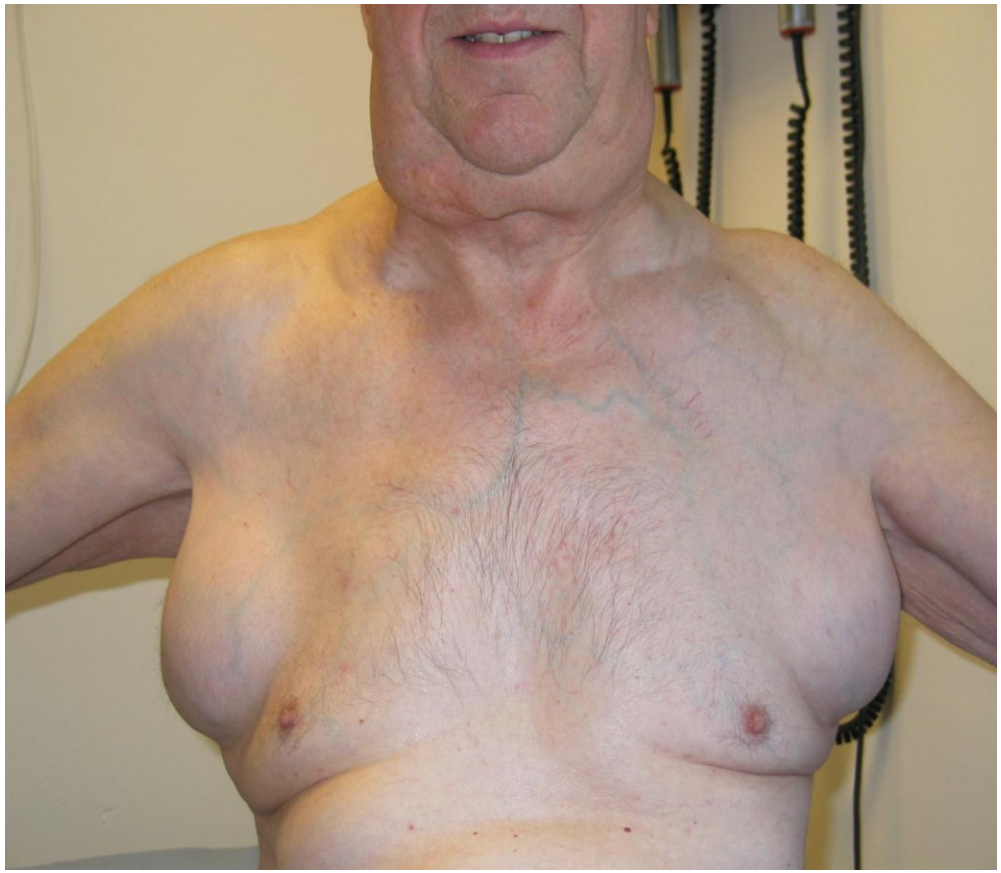
Chronic fatigue , weakness , anorexia, splenomegaly , lymphadenopathy, hepatomegaly.

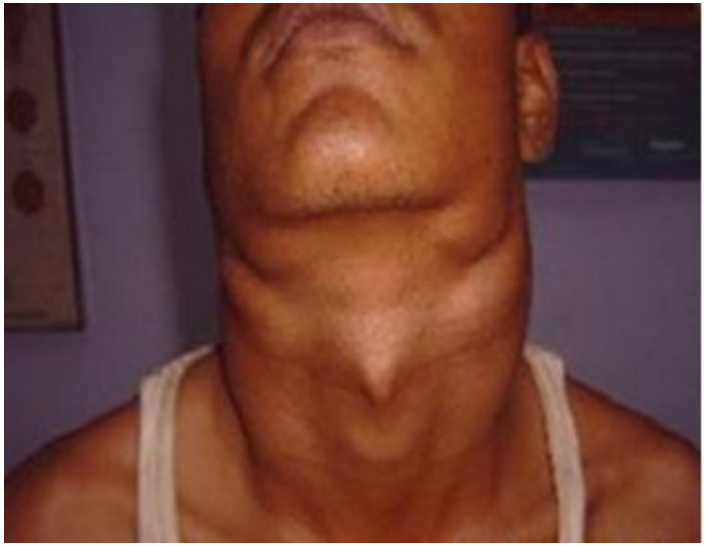
Signs and Symptoms

- Immunosuppression - bacterial infecion.
- Anaemia, Thrombocytopenia.
- Increase blood viscosity and clotting episode

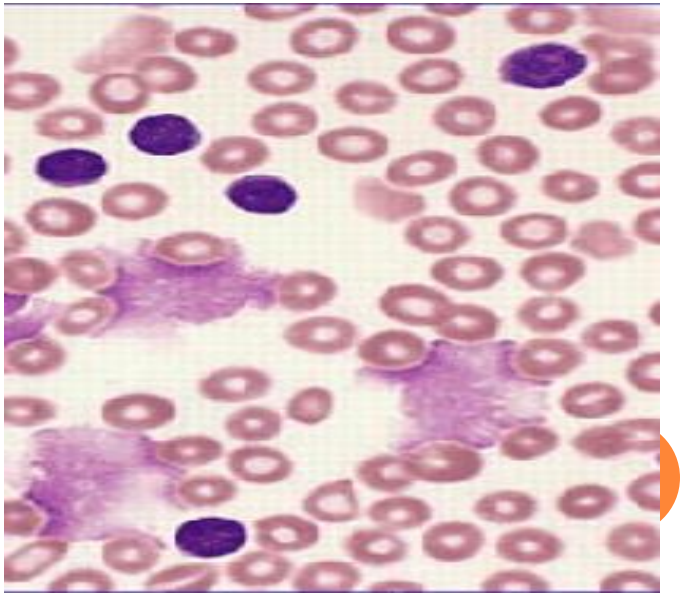
B-CLL CLINICAL SYMPTOMS

Cervical and axillary lymphadenopathy in 60-years old patient with B-CLL





CHRONIC LYMPHOCYTIC LEUKAEMIA/ LYMPHOMA MUST BE DIFFERNTIATED FROM 2ry **REACTIVE LYMPHOCYTOSIS**



CLL - DIAGNOSTIC FEATURES

a) Blood test	**lymphocytosis ≥ 5G/l (4 weeks)**
b) Morphology	**monoconal population of small mature lymphocyte**
c) B-cell CLL phenotype	**clonal CD5+/CD19+ population of lymphocyte**
d) Markers of clonality	**κ/λ light chain restriction; cytogenetical abnormalities**
e) Bone marrow infiltrate	**> 30% of nuceated cells on aspirate**
f) Lymph node	**diffuse infiltrate of small lymphocye**

RAI CLINICAL STAGING SYSTEM

Stage	Clinical Features at Diagnosis	Median Survival (m)
Low risk		
0	Blood (> 5.000/ul. monoclonal lymphocytes) and marrow (>30%) lymphocytosis	>150
Intermediate risk		
I	Lymphocytosis and enlarged lymph nodes	> 101
II	Lymphocytosis and enlarged spleen and/or liver	> 71
High risk		
III	Lymphocytosis and anemia (Hgb < 10g/dL)	> 19
IV	Lymphocytosis and thrombocytopenia (Plt < 100.000/ul.)	> 19

BINET CLINICAL STAGING SYSTEM

Stage	Clinical Features at Diagnosis	Median Survival
A	Blood (> 5.000/ul. monoclonal lymphocytes and marrow (>30%) lymphocytosis and less than 3 areas of palpable lymphoid-tissue enlargement	> 84
B	Lymphocytosis and 3 and more areas of palpable lymphoid-tissue enlargement	< 60
C	Lymphocytosis with anemia (Hgb <10g/dL; or thrombocytopenia (Plt <100.000/uL)	

Markers of poor prognosis in CLL

- Advanced stage (Rai or Binet)
- Peripheral lymphocyte doubling time <12 months
- Raised LDH
- Diffuse marrow histology
- Increased number of prolymphocytes
- Poor response to chemotherapy
- High β2- microglobulin level
- Abnormal karyotyping
- Unmutated VH immunoglobulin gene

Treatment of leukemias

- There are four general types of therapy
  - Chemotherapy – usually a combination of drugs is used
  - Bone marrow transplant
  - Radiotherapy
  - Immunotherapy – stimulate the patients own immune system to mount a response against the malignant cells
  - Monoclonal antibodies – examples include Rituxin

- There are 2 goals:
  - Eradicate the leukemic cell mass
  - Give supportive care

Introduction to leukemia

- Comparison of acute and chronic leukemias:

	Acute	Chronic
Age	all ages	usually adults
Clinical onset	sudden	insidious
Course (untreated)	6 mo. or less	2-6 years
Leukemic cells	immature >30% blasts	more mature cells
Anemia	prominent	mild
Thrombocytopenia	prominent	mild
WBC count	variable	increased
Lymphadenopathy	mild	present;often prominent
Splenomegaly	mild	present;often prominent